

ATTACHMENT A

Validation and Routine Control Recommendations for Reprocessing Medical Devices Labeled as Single Use

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Introduction

The purpose of this document is to provide recommendations for validating the reprocessing of single use devices. This document lists the recommended general requirements for the validation and routine control of reprocessing medical devices labeled as single use to ensure that they remain safe and effective for their intended use. These validation requirements should be required for each original device type from each original equipment manufacturer to ensure that these devices can be safely and effectively reprocessed. Where specific features of a device model within an original equipment manufacturer's device type affects the reprocessor's ability to safely and effectively clean, sterilize, and ensure the functional performance of the device, FDA should also require a separate 510(k) submission or premarket report application.

AdvaMed further urges FDA to review all data relating to cleaning and sterilization, and their affect on device function based on the maximum number of uses in 510(k) submissions. For premarket reports, consistent with the statutory requirements of Sec. 302 of the Medical Device User Fee and Modernization Act (MDUFAMA), AdvaMed urges FDA to review all the data that they would normally review for a premarket approval application, except that for the manufacturing section, FDA should review "a full description of the methods used in, and the facilities and controls used for, the reprocessing and packing of the device."¹ In addition, equipment qualification data is clearly within the purview of the quality system regulation and should be reviewed as part of the quality system inspection process for both 510(k)s and premarket reports.

For purposes of this document, the usual concept of validation applies. That is, validation requires that data must be based on a sufficient statistical sample and includes a minimum of three lots.

Validation and Routine Control Recommendations

1. Cleaning and Sterilizing Process Characterization

The critical first step in any validation program is characterization of the cleaning and sterilization process. Characterizations of the cleaning and sterilization processes must:

- Consider the longest elapsed time between devices' first use and the time cleaning is performed, including transportation, and after each use up to the maximum number of reprocessings.
- Select cleaning agents that are compatible with the device components and well-characterized for organic soil removal throughout the device, including the interior surfaces. This testing should include destructive evaluation of the devices to quantify any internal residual soil.

¹ Section 302(c)(2)(A)(vii) of H.R. 5651, the Medical Device User Fee and Modernization Act of 2002.

- Select soils and perform simulated soiling to closely simulate the contamination in actual clinical use and drying times during collection and shipping until cleaning begins.
- Demonstrate the removal of the soil and cleaning residual from the device through analytical measurements.
- Demonstrate the microbicidal effectiveness as well as the factors which influence
- Microbicidal effectiveness in defining the sterilizing processes. To demonstrate sterilization effectiveness, the worst case sterilization location in or on the device must be identified with half cycle or sublethal exposures. This may require cycle development studies with multiple inoculation and recovery tests.
- Evaluate sterility testing based on consideration of the residual soil that may remain after patient contact, storage and cleaning. Residual organic soils may significantly reduce the lethality kinetics.
- Follow industry standards for sterilization validation and demonstrate that the cycle parameters are capable of producing a sterility assurance level of at least 10^{-6} under worst case sterilization chamber load conditions.
- Consider the effects of the sterilizing agent on materials, device performance, personnel safety, and environmental protection.
- Generate and document specifications for the number of sterilizing cycles allowed. Such specification should include the duration of any stated shelf life.

2. Microbicidal Effectiveness

Studies of microbicidal effectiveness must:

- Demonstrate the lethal action of the sterilizing agent against the type and quantity of soil and microbial contamination expected to be on the device based on the worst case conditions.
- Identify the type of clinical organisms present, and the resistant microorganisms used, for the sterilization method selected.
- Derive an empirical mathematical relationship to define the microbial inactivation kinetics of identified resistant microorganisms.
- Confirm that the probability of a microorganism surviving exposure to a defined treatment can be validly predicted.
- Identify the process variables which affect the lethal action of the sterilizing agent and the interactions of these process variables in relation to this lethal action.
- Assess factors that can adversely influence the effectiveness of the sterilizing agent based upon physical and/or chemical interactions with the device and packaging, including for example, interactions with materials and residues from reprocessing, cleaning and/or disinfection.
- Identify the processing steps employed to remove all residues.
- Identify an analytical test methodology (including sensitivity limits) for residue analysis along with validation data demonstrating the absence of residues.

3. Product Design Considerations

Prior to the reprocessing of a SUD, the design of the predicate device must be considered. Validation testing must:

- Demonstrate that all device materials are compatible with disinfection and sterilizing agents.
- Assess factors that can adversely affect the delivery and/or distribution of the sterilizing agent, including, for example, the environment, packaging configuration(s), geometry, materials and residues from reprocessing, cleaning and/or disinfection.
- Demonstrate that the surface and crevices within the device may be adequately cleaned.
- Demonstrate by analysis that the sterilant has access to all portions, including the inner surfaces and lumens of the device. Such analysis would include, for example, Scanning Electron Microscopy surface analysis of a particular device post sterilization to examine for corrosion, integrity and residual debris.
- Demonstrate that the device's specifications will not be adversely affected by the reprocessing. In the event that the manufacturer responsible for performing the reprocessing (i.e., the Reprocessor) does not have access to the original manufacturer's design specifications, the Reprocessor must define and validate specifications for the device that assure its safety and effectiveness.

4. Package Design Considerations

Factors of the package system that can adversely affect the delivery and/or distribution of the sterilizing agent need to be considered. Validation of the proposed package system must be performed. These validations include:

- Sterility shelf life testing.
- Shipping integrity testing.
- Natural and/or accelerated aging testing.
- Routine testing, including testing of seal strength or packaging.

5. Validation of Cleaning, Disinfection and Sterilization Processes

All equipment used to clean and disinfect devices must be validated and controlled.

5.1 General

The purpose of validation is to demonstrate that established processes are effective and can be consistently reproduced. Validation consists of a number of identified stages: installation qualification, operational qualification and performance qualification. Installation qualification is undertaken to demonstrate that the cleaning and sterilization equipment and any ancillary items have been supplied and installed in accordance with their specification. Operational qualification is carried out either with unloaded equipment or using appropriate test material to demonstrate that the equipment can affect the defined cleaning or sterilization process. Performance qualification is the stage of validation that uses product to demonstrate that equipment consistently operates in accordance with predetermined criteria, and that the process produces product that is clean, sterile, and meets the specified requirements.

5.2 Installation Qualification

Qualification of equipment and installation must:

Equipment

- Establish and document the complete specification of all equipment used to deliver the sterilizing agent, including any ancillary items.
- Demonstrate that the sterilization equipment complies with IEC 61010-1 and any subsequent parts of IEC 61010 that are applicable to the sterilization equipment.
- Establish and document the operating procedures for the equipment. These operating procedures shall include, but are not limited to:
 - a) Step-by-step operating instructions;
 - b) Fault conditions, the manner in which they are indicated, and actions to be taken;
 - c) Instructions for maintenance and calibration; and
 - d) Details of contacts for technical support.

Installation

- Establish and document a specification for the location in which the equipment is to be installed (including any services required) and identify any special precautions and provisions (e.g., safety equipment).
- Document instructions for installation, including instructions pertinent to the health and safety of personnel.
- Confirm, prior to installation qualification, the calibration status of all instrumentation (including any test instruments) used for monitoring, controlling, indicating or recording.
- Demonstrate, after installation, that the equipment and any ancillary items operate as intended.
- If applicable, establish and document conditions for the safe and appropriate storage of the sterilizing agent to ensure that its quality and composition remain within specification.

5.3 Operational Qualification

Prior to operational qualification, the calibration status of all instrumentation (including any test instruments) used for monitoring, controlling, indicating or recording must be confirmed. Operational qualification shall demonstrate that the installed equipment is capable of delivering the specified process within defined tolerances.

5.4 Performance Qualification

- Reprocessors must establish and document the manner of presenting the product for sterilization, including the orientation of product.
- Product used for performance qualification shall be packaged identically to that product that is to be sterilized routinely.
- Generate data to demonstrate the attainment of the defined physical and/or chemical conditions, within specified tolerances, throughout the load and establish the

relationship(s) between the conditions occurring at positions used routinely to monitor the processes. This may be achieved by determining the attainment of the specified condition(s) at predetermined positions throughout the load.

- Conduct microbiological performance qualification studies in which the cleaning or sterilizing agent is delivered under worst case soil conditions designed to reduce the worst case microbial challenge to the process.
- Employ biological indicators that comply with industry recognized standards.
- Perform sterility tests with products subjected to total immersion sterility test conditions as specified in accordance with ISO 11737-2.
- Demonstrate that the levels of any process residues following exposure to the upper tolerances of the process parameters are below the specified limits identified in the health-based risk assessment.
- Confirm that the product meets the specified requirements for safety, quality and performance following application of the defined process at the upper tolerances (and lower when applicable) of the process parameters.

5.5 Review and Approval of Validation

Approval of the sterilization process specifications requires a documented review of the validation data to confirm the acceptability of the sterilization process. The review and approval process must:

- Document and review for acceptability information gathered or produced during installation qualification, operational qualification and performance qualification.
- Confirm that the process specification is complete, including the process parameters and their tolerances. This process specification must also include the criteria for designating an individual process used for a particular product.
- Ensure revalidation of all cleaning and sterilization equipment on an annual basis.

5.6 Revalidation and Equipment Maintenance

All cleaning and sterilization equipment must, at a minimum, be revalidated annually. The purpose of revalidation is to demonstrate that the equipment performs to the parameters detailed in the original validation studies and that no inadvertent changes have occurred. The revalidation must:

- Confirm and document that maintenance procedures are performed as required by the original equipment manufacturer or according to a validated maintenance schedule.
- Confirm and document the procedure for each planned maintenance task and the frequency with which it is to be carried out.
- Confirm and document that equipment is not used to process product until all specified maintenance tasks have been satisfactorily completed and recorded.
- Retain records of maintenance.
- Confirm and document that the maintenance scheme, procedures and records are periodically reviewed by a designated person and that the results of the review are documented.

6. Safety Testing

Devices must be tested to ensure compliance with ISO 10993 – Biological Evaluation of Medical Devices – Part 1: Evaluation and Testing. The testing must demonstrate that adverse leachable substances, including cleaning and disinfection chemicals, do not adversely affect the safety and biocompatibility of the device. Because chemical and material interactions are critical, it is essential to ensure that the tested devices represent all devices being reprocessed, and that the test articles are tested following complete processing. Testing must include an assessment of the level of any residues, (e.g. detergents, lubricants, and germicides) remaining on the medical device after processing, including a toxicological evaluation of these residues.

7. Bioburden and Particulate Testing

There is the potential for used devices to contain a wide range of contaminating microorganisms and residual inorganic and/or organic contamination in spite of the application of a cleaning process. Validation and control of the cleaning and disinfection processes used during reprocessing are therefore essential. To ensure adequate cleaning and disinfection, a program of bioburden and particulate testing must be performed.

Once the cleaning, decontamination and disinfection processes have been thoroughly validated, baseline testing must be performed to determine the level of bioburden on the reprocessed device. A program of bioburden and particulate monitoring should be instituted once the baseline has been established and a consistent level of bioburden and particulates has been achieved following the cleaning process. In addition, the method validation must demonstrate the effectiveness of the test methods for recovery of the bioburden and particulates.

A routine control and monitoring program should be instituted according to industry recognized standards. For example, particular products resterilized with ethylene oxide (EO) should be tested monthly for bioburden and particulate levels following cleaning and disinfection. Corrective action should be performed if products do not meet the limits set in the baseline studies.

8. Pyrogen Validation Testing

Pyrogen testing is material and process dependent. As a result, the product families chosen for validation testing must consist of the same materials and must be processed in the same manner. Products tested as part of routine pyrogen monitoring must be shown not to inhibit and/or enhance the pyrogen test method. Of note, manufacturers may use different materials to manufacture similar type products. As a result, products with similar use but material differences need to be considered separately.

9. Routine Pyrogen Testing

Routine control and monitoring programs should be instituted according to industry recognized standards. Pyrogen tests must include:

- Testing and routine monitoring of feed water used to clean devices.

- Testing and routine monitoring of solutions used to clean devices.
- Testing of devices from each lot that is reprocessed. Tested devices must be representative of all devices within the lot.

10. Routine Monitoring and Control of Processes

Routine monitoring and process control is required to demonstrate that the validated and specified cleaning and sterilization process has been delivered to the product.

- There must be evidence through measurements, supplemented as necessary by biological indicators or chemical indicators that the cleaning and sterilization process was delivered within the defined tolerances.
- There must be recorded data demonstrating the attainment of process parameters.
- Records must be retained in accordance with industry standards.
- The use of any biological indicators in routine monitoring must comply with industry standards.

11. Product Function

Product function controls must include:

- Documentation of process and product flow including any provision for repairing, replacing and/or refurbishing the device or any of its components.
- Design change and control system.
- The validation studies described above.
- An evaluation and rationale based on sound scientific data that each process phase achieves its stated purpose for each process parameter including time, temperature, water and cleaning solution quality, preprocessing conditions, sterilization preconditioning parameters, sterilization cycle parameters, post processing conditions, and control of all critical processing steps.
- A step-by-step process description and rationale for acceptance for the particular device being considered. Process parameters must include, among others, time, temperature, water and cleaning solution quality, preprocessing conditions, sterilization preconditioning parameters, sterilization cycle parameters, post processing conditions, and control of all critical processing steps.
- Validation data establishing maximum number of reuse cycles allowed.

Further Considerations – Prions

Prions are thought to be an abnormal conformation of a normally occurring protein that does not have a nucleic acid genome. Current data suggest that these single proteins alone can act as an infectious agent. A prion has been defined as "small proteinaceous infectious particles which resist inactivation by procedures that modify nucleic acids."²

Prion diseases are often called spongiform encephalopathies because of the post mortem

² Prusiner, S.B.: Prions. In Les Prix Nobel 1997, p. 262-323, 1998. Nobel Foundation, Stockholm, Sweden. Reprinted in Proc. Nat. Acad. Sci. USA 95:13363-13383, 1998.

appearance of the brain with large vacuoles in the cortex and cerebellum. Probably most mammalian species develop these diseases and humans are susceptible to several diseases apparently caused by prions, including: Creutzfeldt-Jakob Disease (CJD), Gerstmann-Straussler-Scheinker syndrome (GSS), Fatal Familial Insomnia (FFI) and Kuru.

Humans may be infected by prions during medical procedures in which contaminated material is either transplanted (e.g., corneal or dura mater transplants) or through contaminated instruments used in neuro-invasive procedures. Thus, while the mechanism of transmission is not well-established or understood, it is nonetheless a concern that must be considered in connection with the reprocessing of single use devices, particularly those used in neuro-invasive procedures.

The inactivation of prions is particularly challenging and traditional sterilization methods that destroy bacteria and viruses do not appear to destroy prions. Prions are extremely resistant to inactivation by ionizing radiation as well as heat and other chemical sterilants. Prions are also unlikely to be susceptible to ethylene oxide sterilization which works by reacting with bacterial cell nucleic acids. Prions are composed of amino acids chains and do not contain nucleic acids.³ As FDA has stated “routine materials and processes that destroy traditional human and animal pathogens do not appear to destroy prions. Presently, no established methods can reliably decontaminate or sterilize articles contaminated with prions.”

³ Block, S.S. “Disinfection, Sterilization, and Preservation”. Lea & Febiger Publisher.: 436438, 4th Addition 1991.

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ISO 11138-1, *Sterilization of health care products — Biological indicators — Part 1: General.*

ISO 11737-1, *Sterilization of medical devices — Microbiological methods — Part 1: Estimation of population of microorganisms on products.*

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